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## Muscle weakness causes joint degeneration in rabbits

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### Summary

*Objective*: The objective of this study was to investigate the effects of botulinum toxin type-A (BTX-A) induced quadriceps weakness on micro-structural changes in knee cartilage of New Zealand White (NZW) rabbits.

*Design*: Fifteen rabbits were divided randomly into an experimental and a sham control group. Each group received a unilateral single quadriceps muscle injection either with saline (sham control; $n = 4$) or BTX-A (experimental; $n = 11$).

*Results*: BTX-A injection produced significant quadriceps muscle weakness ($P < 0.05$) and loss of quadriceps muscle mass ($P < 0.05$). Degenerative changes of the knee cartilage, assessed with the Mankin grading system, were the same for the injected and non-injected hind limbs of the experimental group animals. Sham injection had no effect on joint degeneration but all control animals showed some degenerative changes in the knee. Degenerative changes of the retro-patellar cartilage were more severe in the experimental compared to sham control group rabbits ($P < 0.05$). The distal region of the retro-patellar cartilage was more degenerated than the proximal part in the experimental and control group rabbits ($P < 0.05$). The Mankin grades for the tibiofemoral region were not significantly different between experimental and control group rabbits ($P > 0.05$).

*Conclusion*: Quadriceps muscle weakness caused increased degeneration in the retro-patellar cartilage of NZW rabbits, providing evidence that muscle weakness might be a risk factor for the onset and progression of osteoarthritis (OA). Future work needs to delineate whether muscle weakness directly affects joint degeneration, or if changes in function and movement execution associated with muscle weakness are responsible for the increased rate of OA onset and progression observed here.
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*Key words*: Cartilage, Degeneration, Quadriceps weakness, Knee joint, Histopathology.

### Introduction

Osteoarthritis (OA) is one of the most prevalent chronic musculoskeletal disorders in Canada. It affects approximately 10% of the adult Canadian population[1,2]. It causes pain and disability and is associated with a substantial economic burden and serious socioeconomic consequences[3–6].

The etiology of OA is thought to be multi-factorial and pathological changes may take place in different tissues of joints. OA studies have mainly focused on the changes occurring following intra-articular derangement such as ligament transection[7] or meniscectomy[8]. Little is known on how changes in periarticular structures, such as skeletal muscles, may affect the fully intact joint.

Muscles and joints are functionally interdependent, as muscles move the joints, contribute to joint stability[9], and provide shock absorption[10,11]. Muscles are also the biggest contributors to the mechanical loading of joints which is thought to provide crucial mechanical stimuli for joint integrity and cartilage nutrition[12,13]. Muscles are also implicated in providing proprioceptive information to joints[14]. The motor and sensory functions of muscles are integrated to generate a neuromuscular protective mechanism that allows safe, smooth, functional movements[15,16].

Muscle weakness is an acknowledged associate of joint degeneration and OA, and previous studies have provided evidence that muscle weakness might be an independent contributor to the initiation and development of OA. Muscle weakness is one of the earliest symptoms in patients with OA[17,18]. Also, OA has been associated with reduced muscle strength, decreased activation, and abnormal contraction patterns[17–23]. Moreover, major causes of OA, such as joint injuries, aging and obesity, are accompanied by a loss of muscle mass, strength and fine movement control making joints more susceptible to fatigue[24–27].

Muscle weakness was found to be a better predictor of joint disability and OA[6,23,26,28] than radiographic assessment[29]. These findings suggest that impaired sensorimotor function plays a significant role in the development and progression of OA[15,16,30,31]. However, the possible role of muscle weakness in the development and progression of joint degeneration leading to OA remains unclear. Herzog and Longino[32] developed a quadriceps weakness model in the New Zealand White (NZW) rabbit and found evidence of articular cartilage reddening which was interpreted as an early sign of cartilage deterioration. However, no histological assessment of the joint surfaces or molecular biology approaches of the cartilage were performed to strengthen the "clinical" observation. Therefore, the purpose of this

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study was to investigate the histopathological changes in the rabbit knee following a period of systematic knee extensor weakness. We hypothesized that muscle weakness is associated with degenerative changes in the knee cartilage, thereby providing evidence that muscle weakness might be an independent risk factor for joint degeneration leading to OA.

## Methods

### EXPERIMENTAL DESIGN

Fifteen skeletally mature, 1-year-old, female NZW rabbits (4.75–5.75 kg, *Riemens, St. Agatha, Ont., Canada*) were obtained and studied with the approval of the Animal Care Committee of the University of Calgary. All animals were housed locally in accordance with the Canadian Council on Animal Care Guidelines. Rabbits received a standard diet and water *ad libitum* and were allowed normal activity in individual cages (65 × 45 × 30 cm). The animals were divided randomly into two groups:

(1) Sham controls: 4 weeks post saline injection ($n = 4$).
(2) Experimental rabbits: 4 weeks post single botulinum toxin type-A (BTX-A) injection ($n = 11$).

### INJECTION PROTOCOL

The BTX-A group received a one-time intramuscular BTX-A injection into the quadriceps muscle. The total dose given to each animal was 3.5 units/kg. A 100 unit vial of vacuum-dried *C. botulinum* type-A neurotoxin complex (*Botox, Allergan, Inc., Toronto, Ontario, Canada*) was reconstituted with a 0.9% sodium chloride (without preservatives) to a concentration of 20 units/ml. Prior to the injection, the rabbits were sedated with a 0.18 ml subcutaneous injection of Atravet (10 mg/ml) (*Acepromazine, Ayerst Laboratories, Montreal, Quebec, Canada*). Then, general anesthesia was induced and maintained using a blend of oxygen, nitrous oxide and 1% isoflurane. BTX-A injections were given, at random, either to the right or left quadriceps, as described earlier[33,34]. Briefly, the anterior compartment of the thigh, containing the quadriceps muscle, was isolated by manual palpation. Then the quadriceps was divided visually into superior and inferior halves. Each half was further divided into medial, central and lateral sections. One-sixth of the total BTX-A dose was injected into each of the six sections using a 30-gauge needle.

The sham control animals received injections of a 0.9% sodium chloride solution using an identical procedure and an equal injection volume as that used for the experimental animals. Experimental and control animals were then left alone for 4 weeks, when the outcome measures were determined.

## Outcome measures

### ISOMETRIC KNEE EXTENSOR TORQUE

For the experimental and control group rabbits, muscle weakness was calculated as the percentage difference in knee extensor torque between the injected and contra-lateral non-injected hind limbs. Knee extensor torques were obtained by electrical stimulation of the knee extensor muscles using bilateral femoral nerve cuff stimulators that were implanted immediately prior to testing, as described earlier[33,34].

Knee joints were fixed with two stainless steel bone pins (5 mm diameter) with sharpened tips. The bone pins were inserted from either side into the lateral and medial femoral condyles, respectively. These pins were then clamped to a stereotaxic frame specifically designed for rabbit knee joint testing.

Torques were measured with a tibial restraining bar made of stainless steel and implemented with strain gauges at the distal end that were configured in a Wheatstone bridge configuration[33,34]. The strain gauges in this system can distinguish forces of 0.1 N and the frequency response is 60 Hz which is sufficient for the isometric measurements performed here.

Calibration of the tibial restraining bar was made by applying 10 known forces to the bar and measuring the corresponding voltage output. Linear regression analysis revealed values of $r > 0.999$ between voltage and applied force for the relevant measurement range.

Maximum isometric knee extensor torques were recorded from each hind limb for knee angles of 75°, 100°, and 125° using single twitches and 0.5 s contractions with stimulation frequencies of 10, 50, 100, and 200 Hz (Fig. 1). Torque measurements were repeated for the twitch and 100 Hz contractions at the start and end of each series of tests at a given knee angle to assess fatigue. All measurements were done by an independent tester who was blinded to the side of BTX-A or saline injection and the grouping of the rabbits (experimental and control).
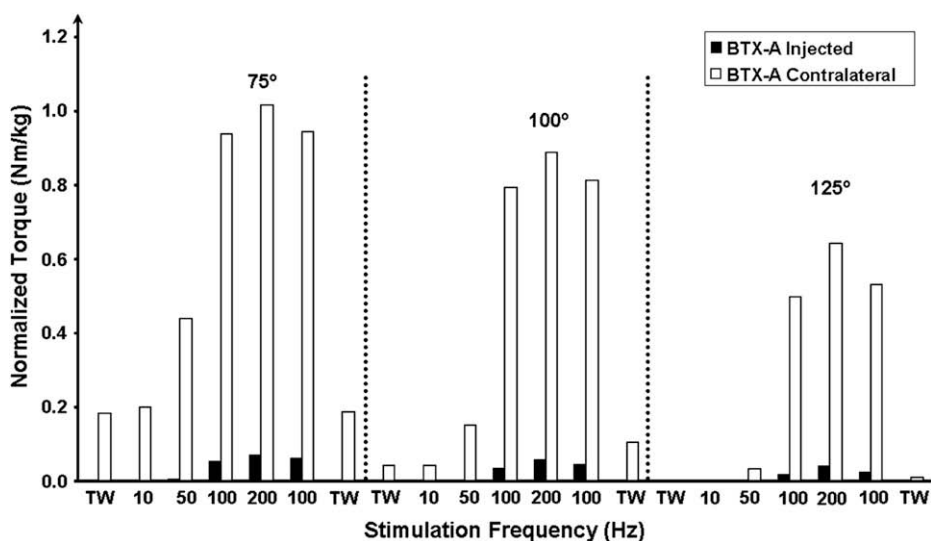


Fig. 1. Torques recorded from the quadriceps muscles of an experimental rabbit (BTX-A injected and its contra-lateral side) at three different knee angles (75°, 100°, 125°). There is a clear and distinct decrease in muscle torque in the Botox injected compared to the contra-lateral hind limb. Tw = twitch contraction, 10, 50, 100 and 200 refer to 10, 50, 100 and 200 pulses of stimulation per second of the femoral nerve which innervates the quadriceps muscles.

All measurements (including the repeat tests at 100 Hz and the single twitches) were used for analysis. Torque reported represents the percent difference between hind limbs.

## QUADRICEPS MUSCLE MASS

Immediately following the knee extensor testing, rabbits were sacrificed by a lethal dose of *Euthanyl* (Pentobarbital sodium injection; *Biomeda-MTC pharmaceuticals, Cambridge, Ontario*) into the lateral ear vein. The rectus femoris, vastus medialis and vastus lateralis (VL) muscles from both hind limbs were harvested and their wet masses were determined using a laboratory scale with an accuracy of 0.001 g. Differences in muscle mass are reported as the percent differences between corresponding hind limbs.

## HISTOLOGY ANALYSIS

The OA grade for the knee cartilage was the main outcome measure of our study. For this purpose, the Mankin OA grading system was used[35].

After sacrifice, knee joints were dissected, excess muscles were trimmed away, and joints were fixed in a 10% neutral buffered formalin solution (Fisher Scientific) for 10 days at room temperature. Following formalin fixation, the joints were transferred to a Cal-Ex II decalcifying solution (10% formic acid solution in formaldehyde, Fisher Scientific) and kept at room temperature. The solution was changed daily. After 2 weeks, the joints were cut opened and returned to a fresh decalcifying solution for an additional 2–3 weeks. Decalcification was finished when joints could be cut smoothly and without any grittiness. The joints were then washed thoroughly in running tap water for 2 h. Then, they were processed in an automatic paraffin processor (Leica TP 1020) where they were dehydrated in a graded series of alcohols ranging between 80% and 100%, cleared in xylene and infiltrated in a mixed Paraplast-plus/extra wax (Fisher Scientific). The individual bones of the knee (tibia, femur and patella) were then embedded in paraffin molds and stored at room temperature until they were sectioned.

Serial sections of the knee articular cartilage were cut at 12–15 μm thickness using a Leica RM 2165 microtome. Every third section was collected, adhered to Superfrost Plus slides (Fisher Scientific) and allowed to dry at 40°C for 7 days. Alternate slides were then stained with hematoxylin, Safranin-O, and fast green (Fisher Scientific). Sections were then dehydrated in ethanol, cleared in xylene, and finally cover-slipped with Polymount mounting media (Fisher Scientific) before they were allowed to dry at room temperature for several days.

Sections were viewed on a light microscope (Zeiss Axiostar plus) by two examiners who were blinded to the study design. Examinations were made with a 25× objective for cartilage scoring and a 200× objective to confirm cellular changes. Sections were examined according to the Mankin criteria (Table I)[35]. Scores of the patellae from the two examiners were used to establish the interobserver reliability.

The standard Mankin system assesses surface structure, cellularity, matrix staining and tidemark integrity of the most severe lesion present. The overall Mankin grade ranges between 0 (normal) and 14 (severe OA)[35]. For each joint, the section that showed the most severe OA changes in each of the knee cartilage regions was graded. For the retro-patellar cartilage, surface was divided visually into three thirds (proximal, middle and distal) using a micrometer eyepiece reticule (area = 12.5 × 12.5;

Table I
*Standard Mankin grading system*[35]

| | |
|---|---|
| **I. Structure** | |
| a. Normal | 0 |
| b. Surface irregularities | 1 |
| c. Pannus and surface irregularities | 2 |
| d. Clefts to transitional zone | 3 |
| e. Clefts to radial zone | 4 |
| f. Clefts to calcified zone | 5 |
| g. Complete disorganization | 6 |
| **II. Cells** | |
| a. Normal | 0 |
| b. Diffuse hypercellularity | 1 |
| c. Cloning | 2 |
| d. Hypocellularity | 3 |
| **III. Safranin-O staining** | |
| a. Normal | 0 |
| b. Slight reduction | 1 |
| c. Moderate reduction | 2 |
| d. Severe reduction | 3 |
| e. No dye noted | 4 |
| **IV. Tidemark integrity** | |
| a. Intact | 0 |
| b. Crossed by blood vessels | 1 |

divided in field of 10 × 10, *Zeiss*). For each patella, each region was assigned a grade, and the worst of all grades was used as the worst retro-patellar Mankin grade.

## STATISTICAL ANALYSIS

Due to the small number of independent observations, non-parametric statistical analysis was used. For the isometric knee extensor torque and muscle mass, outcomes were reported as relative percent deficits of the experimental compared to the sham control group rabbits. Comparisons within each of the two study groups were done using the Friedman test followed by the Wilcoxon signed ranks test to determine which variable was significantly different. Comparisons between the experimental and the control groups were done using the Kruskal–Wallis test followed by the Mann–Whitney *U* test to determine the variable that is different. Spearman's rho correlation coefficient was calculated using the two examiner's scores of the patellar cartilage. The level of significance was set at $\alpha = 0.05$ throughout. All statistical tests were done using SPSS 14 (SPSS Inc., Chicago, Illinois, USA).

## Results

Body weight at the start and end of the study was the same for the experimental and control group rabbits. Surgery and injections were well tolerated by all animals. None of the experimental animals showed any signs of toxin overdose, such as ptosis or increased respiratory distress.

## ISOMETRIC KNEE EXTENSOR TORQUE

The BTX-A group had a significantly greater ($P < 0.05$) torque deficit [%] than the control group (Fig. 2). In the experimental rabbits, the average muscle weakness across all knee angles and stimulation frequencies was 80% ($\pm10\%$). In the control rabbits, there was no difference in average strength ($-9\% \pm 15\%$) between hind limbs.
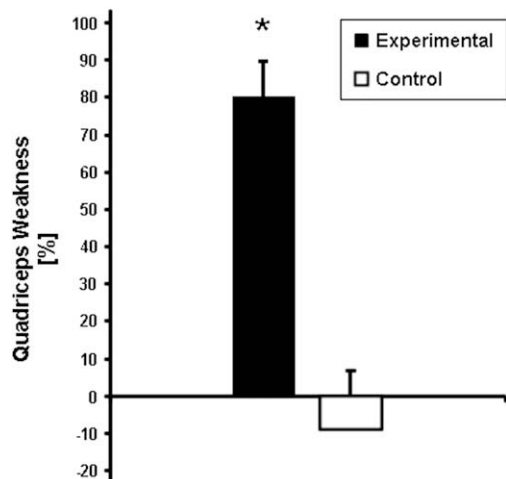
Fig. 2. Percent weakness reflects the relative decrease in torque between corresponding hind limbs in the experimental and the sham control rabbits, averaged across all knee angles and stimulation frequencies tested. Group mean and standard deviation (SD) are shown. The experimental group had a significantly greater weakness [%] than the control group (*$P < 0.05$).

## MUSCLE MASS

Total quadriceps muscle mass deficits were significantly higher ($P < 0.05$) in the BTX-A rabbits ($37 \pm 7\%$) compared to the controls ($2 \pm 9\%$) (Figs. 3 and 4).

## MANKIN GRADES

The knee cartilage from the experimental BTX-A injected ($n = 11$) and control rabbits ($n = 4$) was graded using the Mankin grading system[35].

The Mankin grades of the control rabbits ($n = 4$) were the same for the injected and non-injected hind limbs (Table II). Since muscle weakness was statistically the same between the injected and non-injected hind limbs of the control
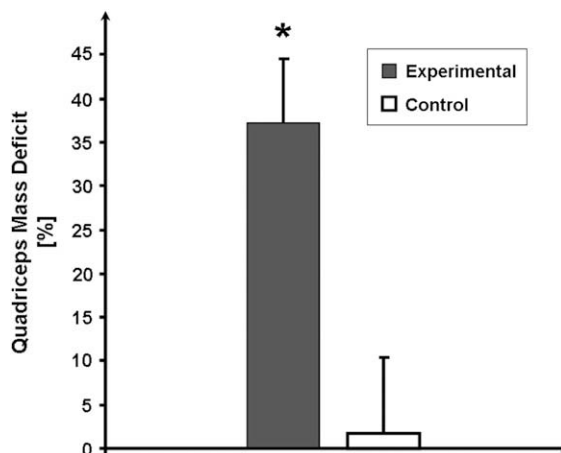


Fig. 3. Percent mass deficit reflects the relative decrease in total quadriceps muscle mass between the corresponding hind limbs in the experimental compared to the sham control rabbits. Group means and SD are shown. The experimental group had a significantly greater total quadriceps muscle mass deficit [%] compared to the control group (*$P < 0.05$).
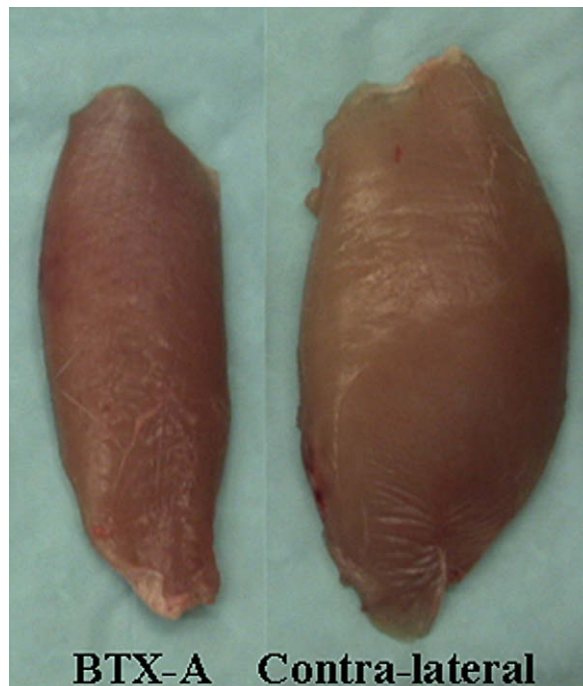


Fig. 4. Example of the VL muscle taken from an experimental BTX-A injected hind limb (Left), and its contra-lateral non-injected side (right). Note the atrophy seen in the BTX-A injected compared to the non-injected contra-lateral side.

rabbits ($P > 0.05$), OA grades from both hind limbs in the control group were pooled ($n = 8$) and the Mankin grades of the control group rabbits were compared to those of the injected ($n = 11$) and non-injected ($n = 11$) hind limbs of the experimental group rabbits.

The worst Mankin grades for the entire patella were significantly higher for the experimental compared to the control group rabbits ($P < 0.05$). Also, Mankin grades for the distal 1/3 of the patella were significantly higher in the experimental compared to the control group ($P < 0.05$). Within each group, there was a location-dependent distribution of the degenerative changes with the proximal 1/3 of the patella showing the least degeneration and the distal 1/3 showing the most degeneration. Specifically for the BTX-A injected limbs, the distal 1/3 of the retro-patellar surface was significantly more degenerated than the middle and proximal regions ($P < 0.05$). For the control group rabbits, the proximal 1/3 showed significantly lower Mankin grades compared to the rest of the patella ($P < 0.05$) (Figs. 5 and 6).

Mankin scores for the entire tibiofemoral joint and for the individual regions of the joint (medial tibia, medial femur, lateral tibia, and lateral femur) were not significantly different ($P > 0.05$) between control and experimental group rabbits (Table II).

## Discussion

The results of this study provide evidence that quadriceps weakness promotes OA progression in the retro-patellar cartilage of NZW rabbits but not in the tibiofemoral cartilage. Interestingly, the degenerative changes between injected (sham or BTX-A) and non-injected hind limbs of the control and the experimental group rabbits were statistically the

Table II

*Mankin grades of the injected and non-injected hind limbs of the experimental and control rabbits. Median and SD of the medial femur, medial tibia, lateral femur, lateral tibia, the retro-patellar cartilage and the worst grade of the knee joint are shown. There were no significant differences in OA grades between hind limbs within each of the two groups*

| Group | Hind limb | Medial femur | Medial tibia | Lateral femur | Lateral tibia | Patella | Worst grade |
|---|---|---|---|---|---|---|---|
| Experimental | Injected | 4.0 (4.4) | 6.0 (3.6) | 0.0 (3.3) | 0.0 (1.2) | 7.0 (1.4) | 9.0 (1.7) |
| | Non-injected | 8.0 (4.3) | 7.0 (2.9) | 0.0 (2.1) | 0.0 (1.8) | 8.0 (2.0) | 9.0 (2.0) |
| Control | Injected | 3.0 (4.9) | 7.0 (3.5) | 3.5 (4.4) | 0.0 (2.5) | 5.0 (2.1) | 7.5 (1.4) |
| | Non-injected | 1.5 (3.2) | 0.0 (3.5) | 0.0 (4.5) | 1.5 (5.2) | 4.0 (3.0) | 8.0 (3.4) |

same for all regions of the knee. The experimental group animals showed significantly higher Mankin scores in the retro-patellar surface region than the control group rabbits. There were location-dependent changes in the retro-patellar cartilage of experimental and control group animals. The proximal regions of the retro-patellar surface always showed less degenerative signs than the distal regions. There were no differences in Mankin scores for any of the regions of the tibiofemoral joint between experimental and control group rabbits.

The higher retro-patellar Mankin scores for the experimental compared to the control group rabbits may be attributed to muscle weakness which interferes with normal loading of the knee. It is known that muscles stabilize joints and contribute significantly to their loading[9,14]. Muscle weakness may result in premature fatigue, reduced limb loading and disuse. The reduced loading may interfere with cartilage nutrition and lead to cartilage degeneration[36,37]. Also, weakness of the quadriceps relative to the hamstrings could have resulted in muscular imbalance and loss of normal co-activation patterns which may have altered normal joint mechanics and contact pressure distribution[38,39]. Moreover, BTX-A-induced muscle weakness might have affected sensory function that might have prevented proper control of joint movement[40,41]. Also, weak muscles are more susceptible to fatigue which, in turn, could lead to reduced proprioceptive acuity[42,43]. Defective quadriceps proprioception could result in inefficient neuromuscular protection of the knee[15,16]. This might have resulted in rapid loading and jarring of the knee and subsequent microtrauma to the articular cartilage[10,11].

The non-injected hind limbs of the experimental group rabbits showed similar degenerative changes as those seen in the BTX-A injected limbs. This finding might be attributed to an increased or altered mechanical loading of the non-injected limbs to compensate for the reduction in muscle force on the experimental side, as observed previously[33,34,44,45].

The results of this study showed a location-dependent degeneration of the retro-patellar cartilage. Experimental and control group rabbits showed more severe signs of OA in the distal and middle regions of the retro-patellar
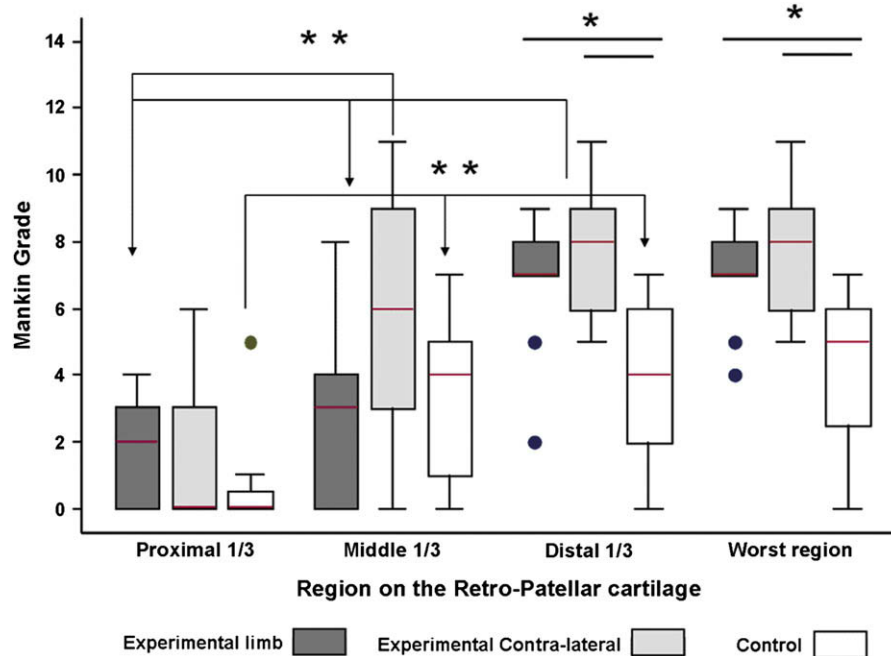


Fig. 5. Box plots showing the Mankin grades of the experimental and control group rabbits. Mankin grades reflected a significant difference in the degenerative changes seen in the entire retro-patellar surface and the distal 1/3 of the retro-patellar cartilage of the experimental compared to control group rabbits (*$P < 0.05$). Within each group, Mankin grades between the different regions of the retro-patellar cartilage were different with the distal part most degenerated and the proximal part least degenerated (**$P < 0.05$).
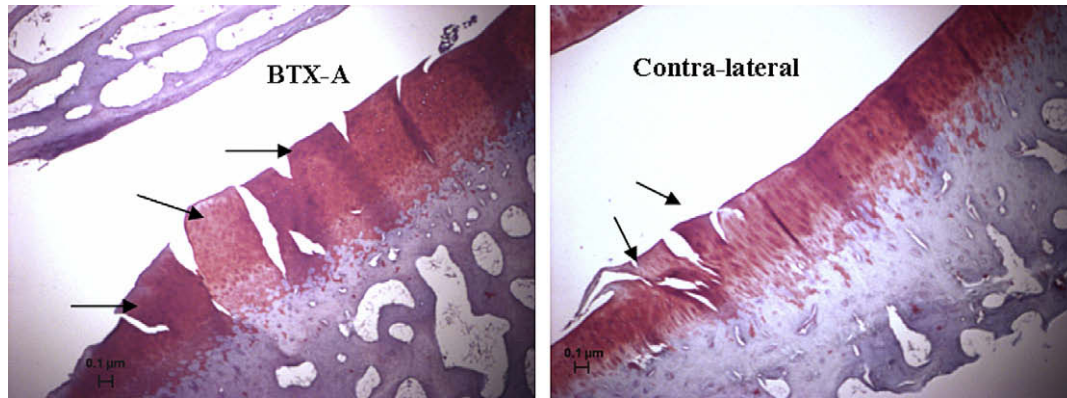
Fig. 6. Sagittal section showing an example of retro-patellar cartilage from (left) an experimental BTX-A injected limb graded with a Mankin grade of 8 and (right) its contra-lateral non-injected side graded as 5. Notice the more severe degenerative changes.

cartilage compared to the proximal region. These location-dependent changes might be attributed to the different contact mechanics in the distal and middle part of the patella compared to the proximal region, or may be associated with location-dependent differences in cartilage structure and/or chondrocyte metabolic properties[46]. There were no significant differences in Mankin scores in the tibiofemoral joints of experimental and control group rabbits.

It is not clear why difference between experimental and control group animals was observed in the patellofemoral but not the tibiofemoral joint. Degenerative changes of the patellofemoral joint were reported to be the earliest changes seen in humans[47] and the most frequent chondral lesion seen in adults[48]. For the current study, we speculate that the degenerative changes in the retro-patellar cartilage are associated with the fact that both the patella and quadriceps muscles are components of the knee extensor mechanism. The quadriceps muscles contribute to the stability and the normal tracking of the patella in relation to the femoral groove[49]. In the Botox-induced quadriceps weakness model in the rabbit, the VL and rectus femoris were found to be more atrophied than the vastus medialis[33,34]. This difference in muscle atrophy may have caused a muscle strength imbalance in the knee extensor group and might have resulted in maltracking of the patella and subsequent changes in the retro-patellar pressure distribution[50,51]. Thus, quadriceps weakness might have had a quicker and a more obvious degenerative effect on the retro-patellar cartilage compared to the tibiofemoral cartilage. Another explanation for the increased degeneration of the retro-patellar cartilage might be associated with location-dependent structural differences of the articular cartilages in different regions of the joint[46,52]. For example, retro-patellar cartilage was found to be thicker and softer than the cartilage in the femoral groove[52–54]. Observations of different macro- and micro-structural properties of cartilages in joints have been published in abundance[54–58]. Further studies are recommended to investigate and explain the location-dependent changes seen in this Botox quadriceps muscle weakness model.

The significantly higher Mankin scores of the retro-patellar cartilage found in the experimental compared to the control group rabbits suggest that quadriceps muscle weakness might be an independent risk factor for knee degeneration, and possibly OA in knee articular cartilage.

Extrapolation of the current results to other joints should be made with caution. Knee stability is greatly influenced by musculature[9,50]. However, this is not necessarily true for other joints, such as the hip, where the bony anatomy provides good stability. How muscle weakness might affect other joints, or knee joints in other species, needs further elaboration.

A limitation of this study was that only one-time point following the creation of muscle weakness was evaluated. Furthermore, this time point was relatively short (4 weeks), and although degenerative changes in the rabbit knee are known to occur quickly following ligament transection[7], or meniscectomy[8], it would be important to follow this model in the long-term and determine if it leads to bona fide OA, or if it merely represents a reversible change of knee morphology.

Furthermore, the muscle weakness simulated in this experimental animal model was restricted to a single muscle group: the knee extensors. Although such muscle weakness can occur due to muscle or peripheral nerve injury, it likely does not represent a large population. General muscle weakness, affecting all or most limb muscles occurs to a great extent in many sub-populations, for example the elderly. Therefore, general muscle weakness, and its effect on joint health, should be studied systematically in the future. Muscle strength in the elderly might delay the onset of idiopathic OA, or might slow its rate of progression. If so, strengthening exercises might provide a low-cost, effective tool to preserve joint health in the elderly and other populations affected by chronic muscle weakness.

A third limitation of this study was the difficulty in interpreting whether the cartilage degeneration observed here resulted directly from the imposed quadriceps muscle weakness, or was merely a consequence of functional changes as a result of the induced muscle weakness. The causes for the degeneration in the retro-patellar cartilage of the BTX-A injected and the non-injected leg of the experimental rabbits might be different: weakness as a direct cause for the degeneration in the injected leg, and compensation for the weakness in the non-injected contra-lateral leg, but the result might be similar as observed here. Nevertheless, the OA muscle weakness model used here causes changes in the patellofemoral joint that are quick and occur in the otherwise fully intact joint. Moreover, in contrast to most other animal models, the knees were permitted full active movement and there was no direct interference with limb loading or joint innervations.

## Conclusion

Unilateral BTX-A-induced quadriceps weakness resulted in increased Mankin scores of the retro-patellar cartilage but not the tibiofemoral joint cartilage in experimental compared to control group rabbits. This result provides evidence that quadriceps weakness is a risk factor that, directly or through its functional implications on joint loading, leads to the onset and progression of osteoarthritic changes in the patellofemoral joint.

## Conflict of interest

None of the authors have anything to disclose.

## Acknowledgments

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